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# Importance of Neuropathological Examination in "Unexplained Stillbirths"

LETTER TO THE EDITOR

Anna Maria Lavezzi

I would like to point out some considerations and provide new insight that may be of interest to readers regarding fetal death, which is currently the most common adverse pregnancy outcome and the leading contributor to perinatal mortality. In developed countries, 1 in 100-200 pregnancies, particularly at or near term, ends in stillbirth. In 2015, there were 2.6 million stillbirths globally, with more than 7,178 deaths per day (1). The reasons of death generally include placental insufficiency, infections, genetic factors, fetal malformations, and maternal health problems. Autoptic investigation, including examination of the placental disk, umbilical cord, and membranes and use of appropriate and standardized diagnostic criteria, is universally considered as a fundamental step to understand the pathogenesis of stillbirths. However, it is well known that intrauterine death remains unexplained in a high percentage of cases (40%-80%) even after a careful autopsy (2). Above all, in these cases, it is very important to perform detailed examination of the autonomic nervous system (ANS) because it can highlight subtle developmental alterations, particularly in brainstem centers that can control basic vital activities, thereby providing a plausible explanation for the interruption of pregnancy.

In 2011, the Stillbirth Collaborative Research Network in the United States has drawn up a detailed neuropathological examination protocol specifically dedicated to determine lesions of ANS with the aim of highlighting the cause of unexplained stillbirths (3).

A specific law ("*Regulations for Diagnostic Post Mortem Investigation in Victims of Sudden Infant Death Syndrome (SIDS) and Unexpected Fetal Death*") has already been in force since 2006 in Italy. This law states that all cases of stillbirths that had suddenly died without any apparent cause after 25 weeks of gestation must be subjected to diagnostic postmortem investigation, in particular, through the use of an appropriate neuropathological protocol, for in-depth analysis of the main nervous centers (4). In our unit, in a 10-year period, the use of this protocol allowed us to identify developmental, morphological, and/or functional alterations in structures responsible for vital activities, mainly those included in the brainstem. These findings provided insight into the specific pathophysiological process leading to prenatal death (5-7).

Both these protocols (American and Italian) also provide essential information that is largely obtained through maternal interviews, mainly about the main risk factors such as maternal smoking during pregnancy. They also provide novel and interesting data about another risk factor, the use of endocrine disruptors (including pesticides) in the area where the mothers live. These harmful agents, in particular, can alter the endocrine status, resulting in deficit in neural connectivity, which is recognized as being responsible for altered development of brain nervous centers (8-10).

In conclusion, I would want to mainly emphasize on the importance, in case of stillbirth, of detailed autoptic investigation (including the examination of ANS) and careful collection of information about risk factors in order to develop preventative strategies for updating the population through public education programs aimed to decrease the incidence of these very devastating events.

"Lino Rossi" Research Center for the Study and Prevention of Unexpected Perinatal Death and SIDS; Department of Biomedical,University of Milan Surgical and Dental Sciences, Milan, Italy

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**Correspondence**
"Lino Rossi" Research Center for the Study and Prevention of Unexpected Perinatal Death and SIDS; Department of Biomedical,University of Milan Surgical and Dental Sciences, Milan, Italy
Phone: xxxxxxxxxx
e.mail:
anna.lavezzi@unimi.it

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